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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/812,393	03/05/1997	LINDA A. SHERMAN	313332000100	2284

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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/812,393	SHERMAN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim 22 has been added. Claims 1-5 and 22 are pending and are under consideration in the instant office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

In the previous response, altering the amino acid sequence of H12 from HLYQGOQW to HLYQGCQVV (amendment filed 1-13-03 and again in the amendment filed 5-9-03) was found to be new matter because it was not readily apparent that "O" should have been "C" or that "W" should have been "VV". In applicants' response filed 3-15-04, H12 was amended back to HLYOGOQW as originally filed. Table 1 and SEQ ID NO:51 are no longer objected to.

Claim Rejections - 35 USC ' 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation "specific... ...for HLA restriction" in the preamble of claim 1 does not have support in the specification as originally filed. Support cannot be found on pg 3, lines 3-22, pg 4, line 1-4, pg 5, line 26, through pg 6, line 7; pg 6, lines 16-20, pg 6, line 23-pg 7, line 25, pg 8, line 3-6, Fig. 13, or the Examples.

The limitation of "cloning or amplifying said nucleic acid molecule comprising a nucleotide sequence isolated from the HLA restricted CTL and encoding..." in claim 1, step c, does not have support in the specification as originally filed. Example 3 teaches cloning α and β chains of TCRs found in CTL recovered from mice that had been administered peptides (starting on pg 12, line 10; see pg 13, line 1). Claim 1, step c, encompasses cloning one molecule that encoding both the α and β chain and cloning a portion of a TCR that comprises an α/β chain variable region without cloning the α/β chain variable region itself.

Fusing any "recovered TCR receptor encoding nucleic acid molecules together to prepare the isolated fused nucleic acid molecule" (claim 1, step e) does not have support in the specification as originally filed. Example 3, pg 13, line 3-6, describe making a chimeric molecule similar to those described hereinabove for clone 4, Fig. 1 and 2, which are limited to four types of chimeric molecules, "two are the dimers obtained as α/ζ + β/ζ and two are single chain TCR/ζ chimeric molecules analogous to those in Figure 1 herein" (pg 8, lines 7-9). In determining whether the phrase has support, it cannot be determined which is the "recovered" portion in Fig. 1. Merely fusing α/β chain variable regions "together" as broadly encompassed by the phrase does not have support in Fig. 1.

Limiting the variable region of the α/β chain to any "functional" variable region (claim 22) does not have support in the specification as originally filed. Support cannot be found on pg 3, lines 3-22, pg 4, line 1-4, pg 5, line 26, through pg 6, line 7; pg 6, lines 16-20, pg 6, line 23-pg 7, line 25, pg 8, line 3-6, Fig. 13, or the Examples. It was well known in the art at the time of filing that the process of cloning was not limited to isolating nucleic sequences encoding variable regions of TCRs specific for the antigen of interest. Limiting the CTL to having any "functional" variable chain α/β chain does not have support.

Claims 1-5 remain rejected and new claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The preamble of claim 1 remains indefinite because the phrase "prepare... ...a nucleic acid sequence encoding at least one of each of the variable regions of the α and β chains" remains indefinite. The claim fails to set forth the structure of the nucleic acid sequence prepared by stating it comprises a nucleic acid sequence of an α chain TCR and a nucleic acid sequence of a β chain TCR. As written, it appears the claim may encompass a nucleic acid molecule encoding each of the possible α chains and each of the possible β chains. It appears as though applicants are attempting to claim making a nucleic acid sequence encoding each of the numerous α chain variable regions of a TCR and each of the numerous β chain variable regions of a TCR. It appears as though applicants are attempting to limit the α chain and β chain to an α chain and β

chain isolated from one particular TCR; however, in reality, the α chain may be from one TCR and the β chain may be from another. The method should result in isolating a nucleic acid sequence comprising a variable region of a TCR α chain and a variable region of a TCR β chain.

Claim 1, step b, as newly amended is indefinite because "said HLA restricted CTL, which contain a nucleic acid molecule comprising a nucleic acid sequence of a variable region of the α chain of the TCR and a nucleic acid sequence of a variable region of the β chain of the TCR" lacks antecedent basis. The previous mention of an HLA restricted CTL was not so limited as in step b. It is unclear if the phrase in step b) --"which contain..."-- is intended to further limit the HLA restricted CTL produced in step a (in which case, the limitation should be in step a), if the phrase is intended to limit the TCRs that are "specific for said TAA" in step a (in which case, the limitation should be in step a) or if the phrase is intended to limit how the CTL are recovered. it is unclear if the phrase "which contain a nucleic acid molecule comprising..." in step b is intended to further describe the TCR of step a) as having an α and β chain, which does not make sense because all TCR have an α and β chain, or if the phrase is intended to further describe nucleic acid sequences cloned in step c) (i.e. cloning a nucleic acid sequence encoding a TCR α chain variable region from the HLA restricted CTL recovered in step b; and cloning a nucleic acid sequence encoding a TCR β chain variable region from the HLA restricted CTL recovered in step b). clarification is required.

Claim 1, step c, as newly amended is indefinite as a whole because the wording of the step is so confusing and does not clearly set forth what nucleic acid sequences

are being cloned or from where the nucleic acid sequences being cloned are isolated. In particular, the phrase "said nucleic acid molecule comprising [sic] nucleotide sequence isolated from the HLA restricted CTL, and encoding..." in claim 1, step c, lacks antecedent basis in claim 1, step b, which requires a "nucleic acid molecule comprising a nucleic acid sequence of a variable region of...." The step does not clearly set forth cloning an α chain variable region of a TCR and a β chain variable region of a TCR on the HLA restricted CTL recovered in step b. It is unclear if appears applicants are attempting to further describe the nucleic acid molecule of step b or if applicants are attempting to describe the nucleic acid sequences cloned in step c.

Claim 1, step d, as newly amended is indefinite because it is unclear if both the α and β chains are recovered. The phrase "said TCR receptor-encoding nucleic acid molecules" lacks antecedent basis. Literal support for the phrase "TCR receptor-encoding nucleic acid molecules" is required when using "said". In addition, use of "TCR" and "receptor" together is redundant because the R in TCR stands for receptor. It is unclear if the phrase "recovering said TCR receptor encoding nucleic acid molecules" refers to recovering the nucleic acid sequence encoding an entire TCR coding region or just the α and β chain variable regions.

Claim 1, step e, as newly amended is indefinite because it is unclear whether "fusing the recovered TCR receptor-encoding nucleic acid molecules" refers to fusing a TCR coding region to another TCR coding region or is limited to fusing a α chain variable region to some other TCR coding regions to make a complete α chain, or to fusing the nucleic acid sequence encoding the α chain variable region to the nucleic

acid sequence encoding the β chain variable region. The phrase "fusion protein, which comprises a variable region of the TCR α chain fused to a variable region of the TCR β chain" does not make sense because fusing a nucleic acid sequence encoding variable region of an α chain TCR with a nucleic acid sequence encoding a variable region of a β chain TCR would not result in a functional TCR; an α variable region and a β chain variable region in one protein is not part of the invention. It is unclear if the phrase is intended to limit the fusion proteins to only the single chain TCR described in the specification on pg 8, line 10-11, Fig. 1, ζ-scTCR and ζ-CD8-scTCR, or if the phrase encompasses any of the single chains that make up the dimer TCRs described on pg 8, lines 9-11 (ζ-Vα, ζ-Vβ, ζ-CD8-Vα or ζ-CD8-Vβ described in Fig. 1).

New claim 22 is indefinite. It cannot be determined whether the phrase "wherein the variable region of the TCR α chain of step e" is limiting the variable region of the TCR α chain of step e to i) only α chain variable regions that function prior to being in the fusion protein or ii) α chain variable regions that function while in the fusion protein. The phrase regarding the β chain is rejected for the same reason. It is unclear if the "function" in claim 22 is limited to the ability to recognize TAA or if the "function" encompasses any function. The phrase "the variable region of the TCR" in claim 22 is unclear because it is unclear if the phrase refers to the variable region of the TCR in step b) or c) or e). it is unclear when the variable region must be functional. It is unclear what function the variable region must possess.

Claim Rejections - 35 USC ' 103

The rejection regarding claims 1-5 under 35 U.S.C. 103(a) as being unpatentable over Man (1994, J. Immunol., Vol. 153, pages 4458-4467) in view of Cole (April 1995, FASEB Journal, Vol, 9, page A801, abstract 4638) has been withdrawn because the combined teachings of Man and Cole did not teach or suggest fusing recovered TCR receptor-encoding nucleic acid molecules together to prepare a fused nucleic acid molecule comprising a sequence encoding a single-chain TCR comprising a fusion protein comprising a variable region of the TCR α chain fused to a variable region of the TCR β chain as in step e of claim 1.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER